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EXAMINER	
GARVEY, TARA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/827,023	BLAZAR ET AL.	
	Examiner	Art Unit	
	Tara L. Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *12-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2004 & 24 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-25 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-11) in the reply filed on April 25, 2006 is acknowledged.

Claims 12-25 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 25, 2006.

Claim Objections

Claim 1 is objected to because of the following informalities: In line 1, the word "producing" is present two times. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the claimed invention are unclear. The claims are directed to a performing a second-generation lineage depletion protocol using two steps. It is unclear what the two steps encompass.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Schuler et al (US 2005/0101012).

Claim 1 is drawn to a method or producing therapeutic regulatory T cells with enhanced suppressive activity comprising selecting a sample of $CD4^+$ T cells, isolating $CD4^+CD25^+$ suppressor T cells from the $CD4^+$ sample and expanding the $CD4^+CD25^+$ T cells ex vivo which results in activating the suppressor activity of the cells and wherein the natural population of $CD4^+CD25^+$ T cells represented a low percentage of the total $CD4^+$ T cell population. Claim 2 further limits the invention to a high level of stringency in the isolation. Claim 3 further limits the inventions to purifying the isolated cells by enhancing the $CD4^+CD25^{bright}$ T cells while depleting $CD25^{dim}$ cells. Claim 4 limits the invention isolation using anti-CD25 conjugated magnetic beads to obtain a cell population with less than 1-2% nonsuppressor cells. Claim 11 limits the invention to the cells being obtained from blood or hematopoietic cells.

Schuler et al teaches isolating $CD4^+$ T cells from human PBMC and isolating the $CD4^+CD25^+$ T cells from the pure untouched $CD4^+$ T cells using CD25 Microbeads

(page 6, paragraph 0077). The selection resulted in a population of $CD4^+CD25^+$ T cells that was more than 95% pure, which can read on a population of cells in which less than 1-2% of the nonsuppressor cells remain in the purified isolate. Additionally, the $CD4^+CD25^+$ T cells comprised approximately 6% of peripheral $CD4^+$ T cells in the blood, which reads on a low percentage of the total $CD4^+$ T cell population (page 7, paragraph 0081). The selection method inherently included using a specified bead to cell ratio, running the composition over a magnetic column to separate cells bound by the microbeads, washing and re-eluting the cells over a second column as evidenced by the protocol for the CD25 Microbeads from Miltenyi Biotech (see page 2), which were disclosed as being used by Schuler et al (page 6, paragraph 0077). The isolation method disclosed by Schuler et al results in a high level of stringency and in enhancement of the $CD4^+CD25^{bright}$ T cells as evidence by the instant specification (page 52) which disclose using the CD25 Microbeads from Miltenyi Biotech. After isolating the $CD4^+CD25^+$ T cells, the cells were expanded, activated and stimulated ex vivo and were shown to exhibit suppressive activity. The reagents used for the expansion of the cells includes anti-CD3 and anti-CD28 monoclonal antibodies in combination with IL-2 (page 2, page 3, paragraphs 0036-0040 and 0043-0044, page 4, paragraphs 0049 to page 5, paragraph 0051 and 0058-0063, page 7, paragraph 0083, lines 23-29 and paragraph 0085 to page 8, page 8, right column, lines 5-11 and paragraph 0090 and page 9). Thus, Schuler et al teach all that is recited in the instant claims.

Claims 1-3, 5 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Roncarolo et al (US 2004/0173778).

Claims 1-3 and 11 have been described previously. Claim 2 further limits the invention to a high level of stringency in the isolation. Claim 3 further limits the inventions to purifying the isolated cells by enhancing the $CD4^+CD25^{bright}$ T cells while depleting $CD25^{dim}$ cells. Claim 5 further limits the invention to activating the isolated cells by a second-generation lineage depletion protocol using two steps and cleavable, antibody-coated, magnetic microbeads.

Roncarolo et al teaches a method of isolating suppressive $CD4^+CD25^+$ T regulatory (Tr) cells comprising purifying $CD4^+$ T cells from PBMC using anti-CD4-coupled microbeads, separating $CD25^+$ cells from the isolated $CD4^+$ T cells using PE coupled anti-CD25 mAbs followed by addition of anti-PE coupled magnetic beads (page 2, paragraphs 0011 to –17, page 7, paragraph 0063 and page 10). The isolation resulted in a population of cells with purity greater than 98 percent (page 3, paragraph 0027). The $CD4^+CD25^+$ Tr cells were cloned. The $CD4^+CD25^+$ Tr cells can be expanded in vitro while maintaining their suppressive effects. The $CD4^+CD25^+$ Tr cells were stimulated, activated and able to proliferate when cultured with a combination of anti-CD3 mAb, soluble anti-CD28 mAb and IL-2 (page 2, paragraph 0026, page 3, paragraphs 0033 to 0035, page 4, paragraphs 0037 to 0038, 0042-0046, page 5, paragraphs 0047 and 0050 and page 7, paragraphs 0064 to 0065). The cell clones were then selected for their constitutively high expression of CD25 by FACS sorting, purified $CD25^{bright}$CD4+ Tr cells (page 2, paragraph 0016, page 5, paragraphs 0052 to

page 6, paragraph 0056). The sorting for $CD25^{bright}CD4+$ Tr cells would inherently result in the depletion of $CD25^{dim}CD4+$ Tr cells. Additionally, the $CD4^+CD25^+$ T cells comprised approximately 2.9% of peripheral $CD4^+$ T cells in the blood, which reads on a low percentage of the total $CD4^+$ T cell population (page 5, paragraph 0053). The cells were maintained in culture for greater than 14 days while maintaining their proliferative and suppressive capacities (page 2, paragraph 0026 to page 3, paragraph 0028). The method taught by Roncarolo encompasses separation of $CD25^+$ Tr cells for the $CD4^+$ cell population using anti-PE coupled magnetic beads that are inherently cleavable, cloning the Tr cells, stimulating the Tr cells and the high expressing cells which are grown in culture for use in therapy (page 2, paragraph 0021) which reads on a method of activating the isolated cells by a two step lineage depletion protocol using cleavable magnetic beads to achieve a cell culture of suppressor Tr cells for therapy. Thus, Roncarolo et al teaches al that is recited in the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roncarolo et al (US 2004/0173778) in view of Diehn et al (PNAS (2002) volume 99(18), pages 11796-11801).

Claims 6-7 further limit the invention to activating the cells with a second generation protocol and cleavable microbeads, the microbeads are coated with antibodies to CD3 and CD28 and the media comprises IL-2. Claims 8 and 9 further limit the invention to the cell expansion being 10-20 fold within 14 days and 100-fold within an additional 1-2 weeks. Claim 10 further limits the invention to the generating suppressor cell lines that retain suppressor function.

Roncarolo et al has been described previously.

Roncarolo et al does not teach using microbeads are coated with antibodies to CD3 and CD28 or explicitly teach that the cell expansion is 10-20 fold within 14 days or 100-fold within an additional 1-2 weeks.

Diehn et al teaches using a 1:1 mixture of anti-CD3 and anti-CD28 coated activated polysterene beads (costimulatory beads) for the stimulation of primary T cells (page 11796, right column, first paragraph and page 11798, left column).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Roncarolo et al to use magnetic beads coated with antibodies to CD3 and CD28 to activate the suppressor regulatory T cells because Roncarolo et al teach that it is within the ordinary skill in the art to expand suppressor Tr cells in vitro culture using a combination of anti-CD3 mAb, soluble anti-CD28 mAb and IL-2 and because Diehn et al demonstrate that primary T cells can be stimulated using microbeads coated with antibodies to CD3 and CD28. Additionally, although Roncarolo et al and Diehn et al do not explicitly teach that the cell expansion was 10-20 fold within 14 days and 100-fold within an additional 1-2 weeks, absent of any evidence to the contrary, one would expect the method taught by the combination of these references would result in this amount of cell expansion over the specified time periods. One would have been motivated to do so in order to receive the expected benefit, as suggested by Diehn et al, of using one reagent to deliver both the anti-CD3 and anti-CD28 antibodies to provide the maximum stimulation to the Tr cells resulting in an expanded culture of suppressor Tr cells for therapy. Absent of any evidence to the contrary, there would have been reasonable expectation of success in using the anti-CD3 and antiCD28 coated microbeads taught by Diehn et al in the method taught by Roncarolo et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 10 and 14 of copending Application No. 11/226,168. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a method of isolating and expanding $CD4^+CD25^+$ regulatory T cells. The claims of the instant application do not specifically claim that the Treg cells are phenotypically $CD45RA^+$, but the specification indicates that the population of $CD4^+CD25^+$ regulatory T cells isolated and expanded by the claimed method are $CD45RA^+$ cells (see page 8, paragraph 0025).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a

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Tara L Garvey, Ph.D.
Examiner
Art Unit 1636

TLG

CELINE QIAN, PH.D.
PRIMARY EXAMINER